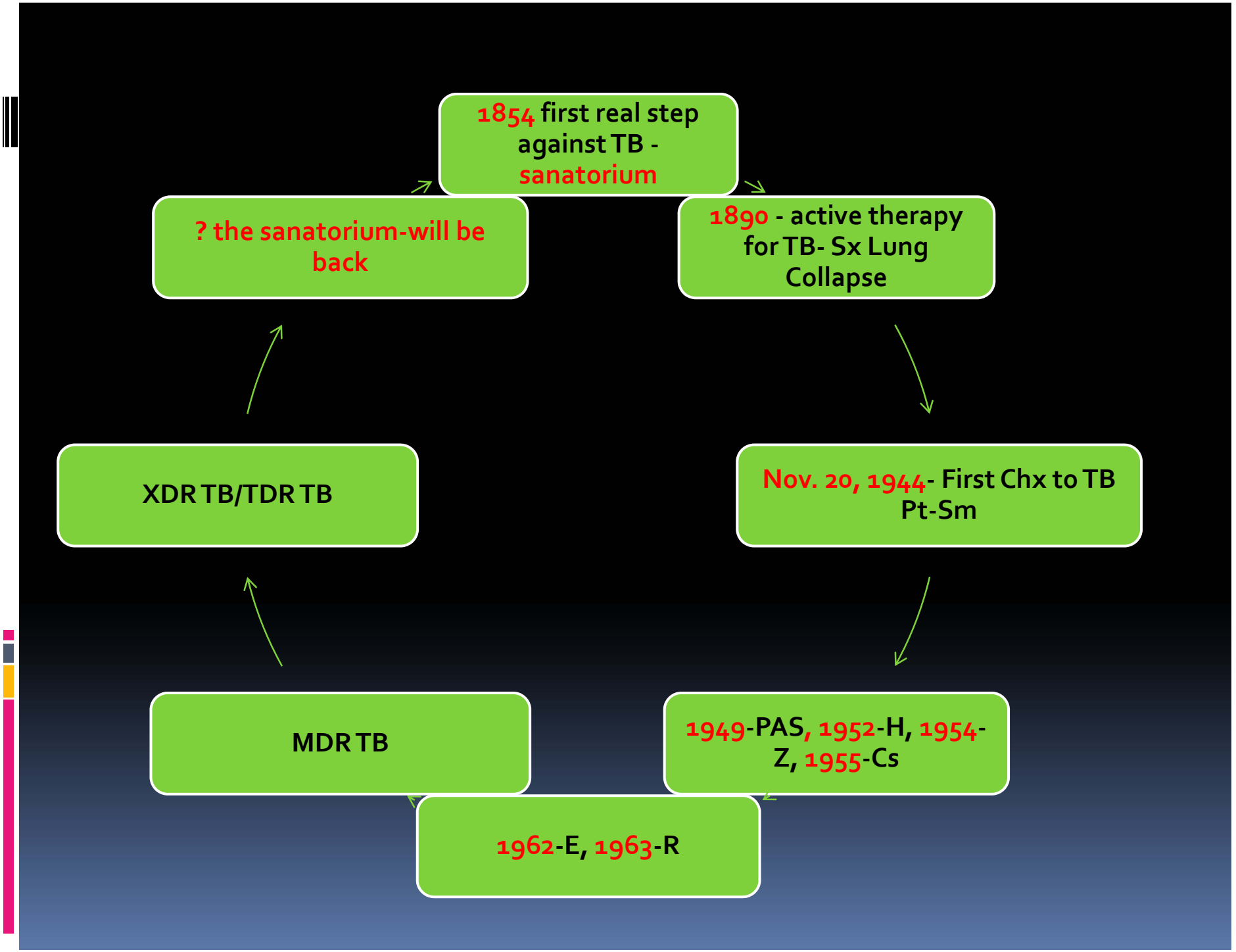
Dr Devendra S. Dadhwal
08-03-2013

NEW DRUGS FOR TUBERCULOSIS

Introduction

- *Mycobacterium tuberculosis* has been present in the human since antiquity - fragments of the spinal column from Egyptian mummies from 2400 BC show definite signs of tuberculosis


1854 first real step against TB - sanatorium
1890 - active therapy for TB- Sx Lung Collapse
Nov. 20, 1944- First Chx to TB Pt-Sm
1949-PAS, 1952-H, 1954-Z, 1955-Cs
1962-E, 1963-R
MDR TB
XDR TB/TDR TB
? the sanatorium-will be back

- Why new anti-TB drug has not been developed and licensed for treatment during the past 50 years?

- Because
  - The economic profile was not sufficient for a drug to be sold to patients who mainly originate from developing world.

- In 1980 the steady drop in TB incidence began to level off or even began to increase in industrialized countries.
- This rise was attributed to a high rate of immigration from high TB incidence countries with the great influence of HIV infection.
- Over 50% of deaths among HIV- infected patients results from co-infection with M. tb
- The two pathogens inducing each other's replication.

Cole and Alzari, Biochemical Society Transactions,
Vol. 35, Part 5 (Sep 2007), pp. 1321-1324. ISSN: 0300-5127

- So New Effective Anti- TB Drugs are need of time

Targets for Anti-TB drugs

- Cell wall biosynthesis
- Mycolic acid biosynthesis
- Energy production
- Amino acid biosynthesis
- Cofactor-related drug targets
- DNA metabolism
- Menaquinone biosynthesis

- Cell wall biosynthesis related targets
  - The cell wall of M. tuberculosis is very important for its survival within constrained conditions
  - The cell wall biosynthetic enzymes do not have homology with the mammalian system

Eoh H et al, Tuberculosis,Vol. 89, No. 1 (Jan 2009), pp. 1-11

  - Peptidoglycan biosynthesis= alanine racemase and D-Ala-D-Ala-ligase catalyze inhibited by D-cycloserine
  - The pyridoxal 5'-phosphate containing enzyme Alr that catalyzes the racemization of L-Alanine into D-Alanine Arabinogalactan biosynthesis

- Mycolic acid biosynthesis related targets
  - These are essential structural components of the mycobacterial cell wall - the site of action of INH and ethionamide
  - M. tuberculosis has both types of fatty acids synthase (FAS) systems found in nature
    - FAS I is the system responsible for de novo synthesis of C16-C26 fatty acids
    - FAS II system extends these fatty acids up to C56 chains to make precursors of mycolic acids

- Energy production related targets
  - Isocitrate lyase (ICL) is involved in energy production via the metabolism of acetyl-CoA and propionial CoA of the glyoxilate pathway
  - But MTB has a salvage pathway
  - So a suitable ATT must target both the main and salvage pathways

- Amino acid biosynthesis related drug targets
  - The shikimate pathway
  - The synthesis of aromatic amino acids
  - It is absent in the mammalian system

    Sarkar et al, Journal of Pharmacy and Pharmaceutical Sciences, Vol. 14, No.2, (Jul 2011), pp. 148-161. ISSN: 1482-1826.
  - Non-aromatic amino acids is also emerging as a potential drug target
  - Lysine , proline, tryptophan and leucine knocked out M. tuberculosis strains showed less virulence

    Pavelka et al, Infection and Immunity, Vol. 71,No.7, (Jul 2003), pp. 4190-4192. ISSN: 0019-9557.

- Cofactor-related drug targets
  - Bacteria synthesize folate de novo but mammals must assimilate preformed folate derivatives
  - Two enzymes involved in the de novo biosynthesis of NAD, can be target for anti-tb drug discovery.
    - The riboflavin biosynthesis pathway
    - The lumazine synthase pathway

Morgunova et al,Biochemistry, Vol. 44, No.8, (Mar 2005), pp. 2746-2758. ISSN: 0006-2960

- DNA metabolism
- Differences in mammalian and mycobacterial DNA metabolism are targets
  - Thymidin monophosphate kinase
  - Ribonucleotide reductases
  - DNA ligases-
    - replication and repair of DNA, liga is essential for growth of M. Tuberculosis
  - DNA gyrase-
    - type IV topoisomerase, its inhibition by fluoroquinolones results in highly mycobactericidal activity

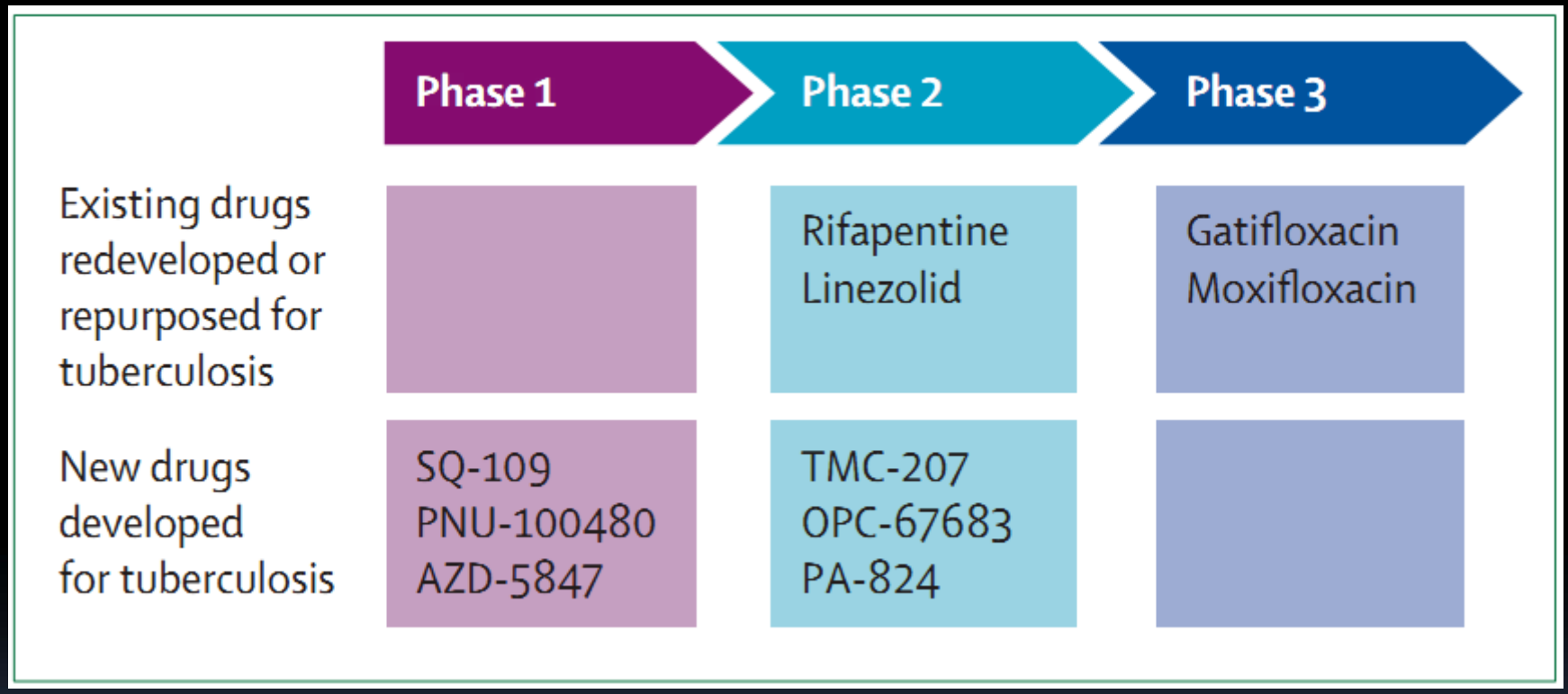
- Menaquinone biosynthesis (vitamin K2)
  - Promising drug target
  - The menaquinone pathway is not present in humans
  - Menaquinone is the only quinone in M. Tuberculosis

Meganathan et al,Vitamins & Hormones, Vol.61, No.173, (Aug 2001), pp. 173-218. ISSN: 0083-6729.

- Other
- MTB cythochrome p450 enzymes- Antifungal azole drugs target these, miconazole and clotrimazole are active against M. tuberculosis
- Peptide deformylase catalyzes- essential for maturation of nascent polypeptides in bacteria but not essential for humans
- Mycothiol synthesis - protection against the damaging effects of reactive oxygen species. This pathway is absent in humans

New Anti-TB drug under trials

- Six classes of drugs
  - Quinolones
  - Nitroimidazoles
  - Oxazolidinones
  - Diarylquinoline (TMC207 Bedaquiline)
  - Ethylenediamine (SQ-109)
  - Rifapentine



AZD-5847, PNU-100480, Linezolid (oxazolidinone), TMC207 (bedaquiline), OPC-67683 (delamanid)

Note: Phase 3 trial of TMC 207 and OPC 67683 are being initiated
TMC 207 got FDA approval for MDR TB

Alimuddin Z et al, NEJM 2013, 368;8; 745-55

Clinical trial

- Phase 0:
  - Pharmacodynamics and Pharmacokinetics
- Phase 1:
  - Screening for safety
- Phase 2:
  - Establishing the testing protocol
- Phase 3:
  - Final testing
- Phase 4:
  - Post approval studies

Quinolones

- Targets
  - DNA gyrase
  - Type IV topoisomerase
    - Eukaryotic cells: No DNA gyrase, have Type II topoisomerase
    - Quinolones do inhibit type II topoisomerase but at higher conc (100-1000 mg/ml)
- Mechanism of action
  - Inhibition of DNA biosynthesis
- Resistance mechanism
  - gyrA mutations
  - Topoisomerase IV genes mutation
  - Transport out drug actively from bacteria

- Bioavailability:50% -95%
- Clearance from body:
  - Most Quinolones by Kidney (Need renal modification)
  - Moxifloxacin & Pefloxacin by Liver (Avoid in hepatic failure)
- Adverse effects
  - GIT
  - CNS: headache dizziness insomnia mood change hallucination delirium seizure NM Blocking
  - Skin: rash, photosensitivity to UV A (lomefloxacin, sparfloxacin)
  - Joint: arthropathy with cartilage erosions, tendon rupture
  - Qtc prolongation: Sparfloxacine>Grepafloxacine>moxifloxacine, gatifloxacine>levo, cipro, oflo
  - Hypo/Hyperglycemia: Gatifloxacine

In Vitro Sn of M.tb to FQs

	MIC90, µg/mL	Cmax, µg/mL	Cmax/MIC
Ciprofloxacin 500mg	0.5-1.0	3.0	3-6
Ofloxacin 400mg	0.5-1.3	4.6	3-9
Levofloxacin 750mg	0.5-1.0	8.6	8-15
Sparfloxacin 400mg	0.25-0.5	1.3	3-6
Gatifloxacin 400mg	0.25-0.5	4.2	8-15
Moxifloxacin 400mg	0.25-0.5	3.2	6
Isoniazid 300mg	0.01-0.06	3-5	20-50

Ginsburg AS et al, Lancet Inf Dis 2003: 3:432-442.

Fluoroquinolones for treating tuberculosis (Review)

Ziganshina LE, Squire SB

THE COCHRANE COLLABORATION®

- Review content assessed as up-to-date: 13 October 2007
- Objectives:

  To assess fluoroquinolones as additional or substitute components to ATT regimens for DS and DR TB

- RCT of ATT regimens containing fluoroquinolones in PTB Spt positive(smear or Culture) were searched.

- Eleven trials (1514 participants) were included in this review

The Cochrane Library 2009, Issue 1

Comparison 1: FQ substituted

	Regimens	Outcome 1 Cure (sputum culture conversion at 8 wk)	Outcome 2 Treatment failure at 12 months.	Outcome 3 Relapse (12 months after cessation of therapy)	Outcome 4 Relapse: by HIV status.	Outcome 5 Time to sputum culture conversion (months)
Mohanty 1993 N=60	2CipSmZH+4CipH vs 2RSmZH+4RH	27/30 vs 25/30 (P = 0.45)	1/30 vs 0/30 (P = 0.50)	3/30 vs 1/30 (P = 0.33)	-	-
Kennedy 1993 N=160	4CipHR+2HR vs 2EZHR+2HRZ+2HR	-	1/81 vs 3/79	-	-	-
Kennedy 1996 N=200	4CipHR+2HR vs 2EZHR+2HRZ+2HR	6/9 vs 11/11 (P = 0.11)	7/82 vs 1/86 (P = 0.24)	7/82 vs 0/86 (P = 0.058)	HIV+ 4/26 vs 0/32 HIV- 3/56 vs 0/54	2.3 (±1.28) No=82 vs 1.8 (±0.77) No=86 MD 0.50 months, 95% CI 0.18 to 0.82
* Burman 2006 N=336	2MoxHRZ vs 2 EHRZ	99/169 vs 98/167 (P = 0.98)	-	-	-	-
Kohno 1992 N=156	9 Ofx HR vs 9 EHR	-	-	0/79 vs 0/77 (P < 0.00001)	-	-
Total events:	Fluoroquinolone vs Basic regimen	132/208 vs 134/208 (P = 0.85)	9/193 vs 4/195 (P = 0.18)	10/191 vs 1/193 (P = 0.022) RR 7.17, 95% CI 1.33 to 38.58	-	-

*moxifloxacin group had significant negative cultures after 4 wk of treatment, shown increased earlier activity (P=0.05)

The Cochrane Library 2009, Issue 1

Comparison 1 FQ substituted

	Regimens	Outcome 6 Time to sputum culture conversion by HIV status (months)	Outcome 7 Clinical or radiological improvement at 8 weeks	Outcome 8 Serious adverse events.	Outcome 9 Total number of adverse events.
Mohanty 1993 N=60	2CipSmZH+4CipH Vs 2RSmZH+4RH		27/30 vs 25/30 (P = 0.45)	1/30 vs 1/30 (P = 1.0)	3/30 vs 3/30 (P = 1.0)
Kennedy 1993 N=160	4CipHR+2HR vs 2EZHR+2HRZ+2HR			3/81 vs 3/79 (P = 0.98)	32/81 vs 36/79 (P = 0.44)
Kennedy 1996 N=200	4CipHR+2HR Vs 2EZHR+2HRZ+2HR	HIV+ No=25 2.9 (1.28) HIV- No= 30 1.7 (0.51)			
Saigal 2001 No=31	2 OfxZHE+10 OfxH vs 2RHE+10 RE			0/16 vs 4/15 (P = 0.12)	
Burman 2006 N=336	2MoxHRZ Vs 2 EHRZ			10/169 vs 8/167 (P = 0.65)	81/169 vs 62/167 (P = 0.047)
Kohno 1992 N=156	9 Ofx HR vs 9 EHR		22/79 vs 31/77 (P = 0.11)	8/79 vs 6/77 (P = 0.61)	10/79 vs 5/77 (P = 0.20)
Total events:	Fluoroquinolone vs Basic regimen		49/109 vs 56/107 (P = 0.69)	22/375 vs 22/368 (P = 0.94)	126/359 vs 106/353 (P = 0.13)

The Cochrane Library 2009, Issue 1

Comparison 2 FQ added to regimen

	regimen	Outcome 1 Cure (sputum culture conversion) at 8 weeks	Outcome 2 Treatment failure at 12 month	Outcome 3 Clinical or radiological improvement at 8 weeks	Outcome 4 Death from any cause.	Outcome 6 Serious adverse events
El-Sadr 1998 No=174	2LfxHREZ+6/9HR vs 2HREZ+6/9 HR	46/87 vs 36/87	6/87 vs 0/87	72/87 vs 73/87	1/87 vs 3/87	21/87 vs 26/87

- Drug-resistance status:
  Resistant areas but MDR-TB or close contact with an MDR-TB were excluded.
- Loss of follow up :
  39% lost to follow up in continuation phase

The trial did not detect a statistically significant difference

The Cochrane Library 2009, Issue 1

Comparison 3 of Lfx vs Ofx

		Outcome 1 Cure (sputum culture conversion) within 2 to 3 wks	Outcome 2 Treatment failure at 12 months	Outcome 3 Clinical or radiological improvement at 8 weeks.	Outcome 4 Total number of adverse events
Lu 2000 No=144 (MDR persumed)	LfxHEZT vs OfxHEZT	59/75 vs 56/69	3/75 vs 2/69	43/75 vs 35/69	11/75 vs 13/69

T=Thioacetazone

The trial did not detect a statistically significant difference

The Cochrane Library 2009, Issue 1

Comparison 4 Spx vs Ofx

Study	Regimen	Outcome 1 Cure (sputum culture conversion within 2 to 3 weeks)	Outcome 2 Treatment failure at 12 months	Outcome 3 Clinical or radiological improvement at 8 weeks.	Outcome 4 Total number of adverse events
Huang 2000 No=104 (MDR)	SpxSmHREZ vs OfxSmHREZ	28/52 vs 8/52	-	50/52 vs 46/52	16/52 vs 10/52
Sun 2000 No=80 (MDR)	SpxHRPto vs OfxHRPto	14/40 vs 11/40	6/40 vs 8/40	34/80 vs 32/80	2/31 vs 3/38
Ji 2001 No=69 (MDR)	2SpxHZ vs 2OfxHZ	-	1/31 vs 4/38	22/31 vs 26/38	5/40 vs 11/40
Total events	Sparfloxacin vs Ofloxacin	42/92 vs 19/92 (P = 0.15)	7 /71 vs 12/78 (P = 0.27)	106 /163 vs 104/170 (P = 0.38)	23 /123 vs 24 /130 (P = 0.94)

The Cochrane Library 2009, Issue 1

- Authors concluded
  - There was no statistically significant difference in trials substituting ciprofloxacin, ofloxacin or moxifloxacin for first- line ATT drugs in relation to
    - Cure
    - Treatment failure
    - Clinical or radiological improvement
  - Substituting ciprofloxacin into first-line ATT inDS PTB should not be used as it causes
    - Higher incidence of relapse
    - Longer time to sputum culture conversion
  - Trials of newer FQs for treating M.tb are needed

The Cochrane Library 2009, Issue 1

Moxifloxacin-containing Regimens of Reduced Duration Produce a Stable Cure in Murine Tuberculosis

Eric L. Nuermberger, Tetsuyuki Yoshimatsu, Sandeep Tyagi, Kathy Williams, Ian Rosenthal, Richard J. O'Brien, Andrew A. Vernon, Richard E. Chaisson, William R. Bishai, and Jacques H. Grosset

PROPORTIONS OF MICE RELAPSING AFTER TREATMENT COMPLETION

	Duration of Treatment (*mo*)						
	3		4		5		6
Treatment	No.	cfu Range*	No.	cfu Range*	No.	cfu Range*	No.
2RHZ/4RH	11/12	2.7–3.7	5/12	2.1–3.4	1/16	0.6	0/12
1RMZ/4RM	4/12	1.7–3.0	0/12	0	0/12	0	Not done
2RMZ/3RM	2/12	0.3–2.9	0/12	0	0/13	0	Not done
5RMZ	4/12	3.4–3.7	0/12	0	0/12	0	Not done

Definition of abbreviations: H = isoniazid; M = moxifloxacin; R = rifampin; Z = pyrazinamide.
*Range of $\log_{10}$ cfu counts in the lungs of relapsing mice.

- RMZ reduced the lung cfu counts more rapidly than did RHZ
- There were similar efficacy for all RMZ-based regimens whether Z was administered for 1 month, 2 months, or the entire duration of therapy
- RMZ (any regimens) achieved stable cure in all mice after 4 months
- The standard regimen (RHZ) required 6 months of therapy for stable cure of all mice.

Am J Respir Crit Care Med Vol 170. pp 1131–1134, 2004

A Phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis

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SETTING: Current treatment for pulmonary tuberculosis (TB) might be shortened by the incorporation of fluoroquinolones (FQs).

OBJECTIVES: A Phase II study aimed to assess the sterilising activities of three novel regimens containing FQs before a Phase III trial of a 4-month regimen containing gatifloxacin (GFX).

DESIGN: A total of 217 newly diagnosed smear-positive patients were randomly allocated to one of four regimens: isoniazid (INH), pyrazinamide and rifampicin (RMP) with either ethambutol, GFX, moxifloxacin (MFX) or ofloxacin (OFX) for 2 months. At the end of the study, RMP and INH were given for 4 months. The rates of elimination of *Mycobacterium tuberculosis* were compared in the regimens using non-linear mixed effects modelling of the serial sputum colony counts (SSCC) during the first 8 weeks.

RESULTS: After adjustment for covariates, MFX substitution appeared superior during the early phase of a bi-exponential fall in colony counts, but significant and similar acceleration of bacillary elimination during the late phase occurred with both GFX and MFX ($P = 0.002$). Substitution of OFX had no effect. These findings were supported by estimates of time to conversion, using Cox regression, but there were no significant differences in proportions culture-negative at 8 weeks.

CONCLUSIONS: GFX and MFX improve the sterilising activity of regimens and might shorten treatment; their progression into Phase III trials therefore seems warranted.

KEY WORDS: pulmonary tuberculosis; randomised clinical trial; modelling; FQs

INT J TUBERC LUNG DIS, 2008, 12(2):128–138

Moxifloxacin versus ethambutol in the initial treatment of tuberculosis: a double-blind, randomised, controlled phase II trial

Marcus B Conde, Anne Efron, Carla Loredo, Gilvan R Muzy De Souza, Nadja P Graça, Michelle C Cezar, Malathi Ram, Mohammad A Chaudhary, William R Bishai, Afranio L Kritski, Richard E Chaisson

Summary

Background New treatments are needed to shorten the time required to cure tuberculosis and to treat drug-resistant strains. The fluoroquinolone moxifloxacin is a promising new agent that might have additive activity to existing antituberculosis agents. We assessed the activity and safety of moxifloxacin in the initial stage of tuberculosis treatment.

Methods We undertook a phase II, double-blind, randomised controlled trial of a regimen that included moxifloxacin in adults with sputum smear-positive tuberculosis at one hospital in Rio de Janeiro, Brazil. 170 participants received isoniazid, rifampicin, and pyrazinamide at standard doses and were assigned by permuted block randomisation to receive either moxifloxacin (400 mg) with an ethambutol placebo (n=85) or ethambutol (15–20 mg/kg) plus moxifloxacin placebo (n=85) 5 days per week for 8 weeks. The primary endpoint was the proportion of patients whose sputum culture had converted to negative by week 8. Analysis was by modified intention to treat (ITT); patients whose baseline cultures were negative, contaminated, or contained drug-resistant *Mycobacterium tuberculosis* were excluded from the analysis. Additionally, all missing 8-week results were deemed treatment failures. This study is registered with ClinicalTrials.gov, number NCT00082173.

Findings 74 patients assigned to the moxifloxacin group and 72 in the ethambutol group were included in the modified ITT population. 125 patients had 8-week data (moxifloxacin n=64, ethambutol n=61); the main reason for absence of data was culture contamination. At 8 weeks, culture conversion to negative had occurred in 59 (80%) of 74 patients in the moxifloxacin group compared with 45 (63%) of 72 in the ethambutol group (difference 17·2%, 95% CI 2·8–31·7; p=0·03). There were 16 adverse events (eight in each group) in 12 patients. Only one event was judged related to study drug (grade 3 cutaneous reaction in the ethambutol group).

Interpretation Moxifloxacin improved culture conversion in the initial phase of tuberculosis treatment. Trials to assess whether moxifloxacin can be used to shorten the duration of tuberculosis treatment are justified.

Note: Bayer Healthcare donated moxifloxacin and matching placebo for the trial, but had no input into the study design, execution, or analysis.

Lancet 2009; 373: 1183–89

Substitution of Moxifloxacin for Isoniazid during Intensive Phase Treatment of Pulmonary Tuberculosis

Susan E. Dorman[1], John L. Johnson[2], Stefan Goldberg[3], Grace Muzanye[4], Nesri Padayatchi[5], Lorna Bozeman[3], Charles M. Heilig[3], John Bernardo[6], Shurjeel Choudhri[7], Jacques H. Grosset[1], Elizabeth Guy[8], Priya Guyadeen[9], Maria Corazon Leus[10], Gina Maltas[1], Dick Menzies[11], Eric L. Nuermberger[1], Margarita Villarino[3], Andrew Vernon[3], Richard E. Chaisson[1], and the Tuberculosis Trials Consortium*

Rationale: Moxifloxacin has potent activity against *Mycobacterium tuberculosis in vitro* and in a mouse model of antituberculosis (TB) chemotherapy, but data regarding its activity in humans are limited.

Objectives: Our objective was to compare the antimicrobial activity and safety of moxifloxacin versus isoniazid during the first 8 weeks of combination therapy for pulmonary TB.

Methods: Adults with sputum smear–positive pulmonary TB were randomly assigned to receive either moxifloxacin 400 mg plus isoniazid placebo, or isoniazid 300 mg plus moxifloxacin placebo, administered 5 days/week for 8 weeks, in addition to rifampin, pyrazinamide, and ethambutol. All doses were directly observed. Sputum was collected for culture every 2 weeks. The primary outcome was negative sputum culture at completion of 8 weeks of treatment.

Measurements and Main Results: Of 433 participants enrolled, 328 were eligible for the primary efficacy analysis. Of these, 35 (11%) were HIV positive, 248 (76%) had cavitation on baseline chest radiograph, and 213 (65%) were enrolled at African sites. Negative cultures at Week 8 were observed in 90/164 (54.9%) participants in the isoniazid arm, and 99/164 (60.4%) in the moxifloxacin arm ($P = 0.37$). In multivariate analysis, cavitation and enrollment at an African site were associated with lower likelihood of Week-8 culture negativity. The proportion of participants who discontinued assigned treatment was 31/214 (14.5%) for the moxifloxacin group versus 22/205 (10.7%) for the isoniazid group (RR, 1.35; 95% CI, 0.81, 2.25).

Conclusions: Substitution of moxifloxacin for isoniazid resulted in a small but statistically nonsignificant increase in Week-8 culture negativity.

Am J Respir Crit Care Med Vol 180. pp 273–280, 2009

- The Cmax to MIC and AUC to MIC ratios of MFX are significant with concomitant RMP ($P<0.001$).
- INH has no significant effect on the pharmacokinetics of MFX

Geetha R. et al, Indian J Med Res 136, December 2012, pp 979-984

- Moxifloxacin is promising drug to short the duration of PTB but need further large study

Nitroimidazoles

- Metronidazole was shown to have bactericidal activity against dormant Mtb.
- In 1989, Hindustan Ciba-Geigy demonstrated the anti-tb activity of these bicyclic nitroimidazoles and they
  - Generated the lead compound CGI-17341
  - Active against DS as well as DR Mtb
  - But further development was abandoned due to its mutagenicity
- More than a decade later, the mutagenicity problem was overcame and
  - PathoGenesis (now Novartis) came out with their lead compound PA-824
  - Otsuka Pharmaceutical, came out with their lead compound OPC-67683

Future Med Chem. 2011 Sept. ; 3(11): 1427–1454

- Nitroimidazoles are active against replicating and non-replicating bacteria
  - May shorten treatment for PTB
  - May used for management of latent TB infection
- Nitroimidazoles are activated by bioreduction for which a low redox potential electron transfer system is required.
- This low redox bioreducction is beyond the reduction capacity of mammalian redox systems.

Future Med Chem. 2011 Sept. ; 3(11): 1427–1454

- Targets:
  - Deazaflavin dependent nitroreductase
- Mechanism of action
  - Rv3547 of MTB a deazaflavin-dependent nitroreductase (Ddn), transforms PA-824 into des-nitroimidazole
    (M. leprae lost of the Ddn gene from the genome)
  - Des-nitro metabolite formation generated reactive nitrogen species (NO)
    - The aerobic killing: inhibit mycolic acid biosynthesis
    - The anaerobic killing: inhibition of cytochrome c oxidase by NO (respiratory chain poison)
- Resistance mechanism
  - Rv0407, Rv3547, Rv3261 and Rv3262 mutations

Future Med Chem. 2011 Sept. ; 3(11): 1427–1454

PA-824

- It a prodrug, metabolized by M. tb before exercising its effect
- Highly specific for the Mtb complex
- The pulmonary aerosol administration of PA-824 in guinea pigs gave as compare to the oral route
  - Lower systemic exposure of the drug
  - Higher lung concentrations of drug

Sung JC et al, Antimicrob. Agents Chemother. 2009; 53(4):1338–1343

- Its maximal plasma concentration reached in 4 to 5 h.
- The average elimination half life 16 to 20 h
- Adverse effects :
  - Elevation of serum creatinine level
    - Dose-dependent, reversible & benign
    - Attributed to the inhibition of tubular secretion of creatinine

- Study in mice demonstrated that
  - PA-824 at 100 mg/kg is equipotent to
    - INH 25 mg/kg
    - Gatifloxacin 100 mg/kg
    - Moxifloxacin 100 mg/kg,

Lenaerts AJ et al, Antimicrob Agents Chemother. 2005; 49(6):2294–2301

- 2PMZ/2PM vs 2HRZ/4HR
  - Able to cure mice faster
  - The absence of relapse 3months after cessation of therapy

Nuermberger E et al. Antimicrob. Agents Chemother. 2008; 52(4):1522–1524.

- Currently it is in phase II clinical trials

ClinicalTrials:PA-824-CL-007

- Phase II 'Evaluation of Early Bactericidal Activity in Pulmonary Tuberculosis'
- Sponsor: Global Alliance for TB Drug Development
- Study Type: Interventional
- Study Design:
  - Allocation: Randomized
  - Endpoint Classification: Safety/Efficacy Study
  - Intervention Model: Parallel Assignment
  - Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
  - Primary Purpose: Treatment

http://clinicaltrials.gov/ct2/show/NCT00567840

- 68 patients with newly diagnosed uncomplicated, smear-positive PTB
  - Intervention group: PA-824 orally at a dose of 200, 600, 1000 and 2000 mg once daily for 2 weeks (No=15 each)
  - Control group: HREZ (No=8)
- EBA measures by the daily reduction in mycobacterial counts in sputum
- Study Start Date: August 2007
- Study Completion Date: December 2007
- Published in :
  - ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2010, p. 3402–3407

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2010, p. 3402–3407 Vol. 54, No. 8
0066-4804/10/$12.00 doi:10.1128/AAC.01354-09

Early Bactericidal Activity and Pharmacokinetics of PA-824 in Smear-Positive Tuberculosis Patients▽†

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PA-824 is a novel nitroimidazo-oxazine being evaluated for its potential to improve tuberculosis (TB) therapy. This randomized study evaluated safety, tolerability, pharmacokinetics, and extended early bactericidal activity of PA-824 in drug-sensitive, sputum smear-positive, adult pulmonary tuberculosis patients. Fifteen patients per cohort received 1 of 4 doses of oral PA-824: 200, 600, 1,000, or 1,200 mg per day for 14 days. Eight subjects received once daily standard antituberculosis treatment as positive control. The primary efficacy endpoint was the mean rate of change in log CFU of *Mycobacterium tuberculosis* in sputum incubated on agar plates from serial overnight sputum collections, expressed as $\log_{10}$ CFU/day/ml (± standard deviation [SD]). The drug demonstrated increases that were dose linear but less than dose proportional in serum concentrations in doses from 200 to 1,000 mg daily. Dosing of 1,200 mg gave no additional exposure compared to 1,000 mg daily. The mean daily CFU fall under standard treatment was 0.148 (±0.055), consistent with that found in previous studies. The mean daily fall under PA-824 was 0.098 (±0.072) and was equivalent for all four dosages. PA-824 appeared safe and well tolerated; the incidence of adverse events potentially related to PA-824 appeared dose related. We conclude that PA-824 demonstrated bactericidal activity over the dose range of 200 to 1,200 mg daily over 14 days. Because maximum efficacy was unexpectedly achieved at the lowest dosage tested, the activity of lower dosages should now be explored.

ClinicalTrials:same

- Similar Phase II study 'Evaluation of Early Bactericidal Activity in Pulmonary Tuberculosis' with lower dose of PA-824 (50, 100, 150 and 200 mg once daily for 14 days)

- Study completed in 2010
- No Study Results Posted

http://clinicaltrials.gov/ct2/show/NCT00944021A

ClinicalTrials:J-M-Pa-Z

- Phase II clinical trials Evaluation of Early Bactericidal Activity in Pulmonary Tuberculosis With(J-M-Pa-Z)
- Sponsor: Global Alliance for TB Drug Development
- Study Type: Interventional
- Study Design:
  - Allocation: Randomized
  - Endpoint Classification: Efficacy Study
  - Intervention Model: Parallel Assignment
  - Masking:Double Blind (Subject, Caregiver, Investigator, O utcomes Assessor)
  - Primary Purpose: Treatment

http://clinicaltrials.gov/ct2/show/NCT01215851

- J=TMC

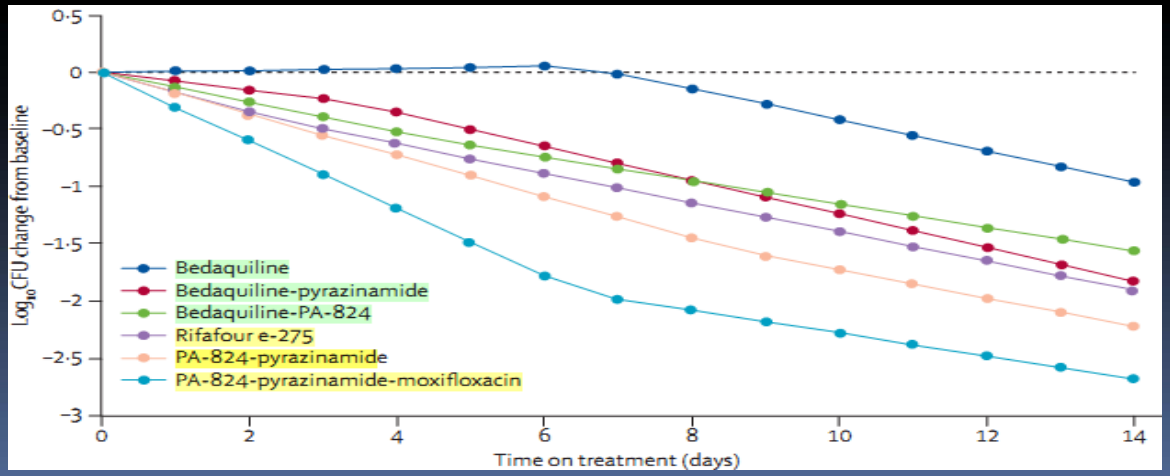
- Intervention
  - PA-824 plus PZA (No=15)
  - PA-824 plus PZA plus moxifloxacin (No=15)
  - PA-824 plus TMC207 (No=15)
  - TMC207 plus PZA (No=15)
  - TMC207 only (No=15)
- A control group would be treated with standard HREZ (No=10)
- The primary outcome was the 14-day EBA assessed in a central laboratory from the daily fall in CFU of M.tb per mL of sputum in daily overnight sputum collections.
- Study Start Date: October 2010
- Study Completion Date: August 2011
- Published in
  - Lancet. 2012 Sep 15;380(9846):986-93.

14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial

Andreas H Diacon, Rodney Dawson, Florian von Groote-Bidlingmaier, Gregory Symons, Amour Venter, Peter R Donald, Christo van Niekerk, Daniel Everitt, Helen Winter, Piet Becker, Carl M Mendel, Melvin K Spigelman

Findings The mean 14-day EBA of PA-824-moxifloxacin-pyrazinamide (n=13; 0·233 [SD 0·128]) was significantly higher than that of bedaquiline (14; 0·061 [0·068]), bedaquiline-pyrazinamide (15; 0·131 [0·102]), bedaquiline-PA-824 (14; 0·114 [0·050]), but not PA-824-pyrazinamide (14; 0·154 [0·040]), and comparable with that of standard treatment (ten; 0·140 [0·094]). Treatments were well tolerated and appeared safe. One patient on PA-824-moxifloxacin-pyrazinamide was withdrawn because of corrected QT interval changes exceeding criteria prespecified in the protocol.

Interpretation PA-824-moxifloxacin-pyrazinamide is potentially suitable for treating drug-sensitive and multidrug-resistant tuberculosis. Multiagent EBA studies can contribute to reducing the time needed to develop new antituberculosis regimens.



Bilinear regression showing the fall in mean log_{10}CFU from baseline

Lancet 2012; 380: 986–93

OPC-67683 (Delamanid)

- It is a prodrug, M.tb metabolizes it and produces as a product desnitro-imidazooxazole metabolite
- It is not metabolized by the cytochrome P450 of liver microsomes of both human and animals
  - There are possibility for it to be used in combination with drugs, including anti-retrovirals.
- It was also found to superior to R, H and PA-824 against Mtb growing in human macrophages even when the exposure was limited to 4 h.

PLOS MEDICINE

OPC-67683, a Nitro-Dihydro-Imidazooxazole Derivative with Promising Action against Tuberculosis In Vitro and In Mice

Makoto Matsumoto[1*], Hiroyuki Hashizume[1], Tatsuo Tomishige[1], Masanori Kawasaki[1], Hidetsugu Tsubouchi[2], Hirofumi Sasaki[2], Yoshihiko Shimokawa[3], Makoto Komatsu[2]

1 Microbiological Research Institute, Otsuka Pharmaceutical, Tokushima, Japan, **2** Medicinal Chemistry Research Institute, Otsuka Pharmaceutical, Tokushima, Japan, **3** Tokushima Research Institute, Otsuka Pharmaceutical, Tokushima, Japan

PLoS Medicine | www.plosmedicine.org

November 2006 | Volume 3 | Issue 11 | e466

IC_{50} of OPC-67683 and INH against Mycolic Acid Synthesis

Compound	Subclass Mycolic Acid and Fatty Acid	IC50 (μg/ml)	95% Confidence Interval (μg/ml)
OPC-67683	Fatty acid	>0.25	—
	α-Mycolic acid	>0.25	—
	Methoxy-mycolic acid	0.036	0.020–0.068
	Keto-mycolic acid	0.021	0.009–0.059
INH	Fatty acid	>4	—
	α-Mycolic acid	1.851	1.109–3.090
	Methoxy-mycolic acid	0.63	0.537–0.738
	Keto-mycolic acid	0.69	0.422–1.129

The IC_{50} (concentration required to inhibit activity by 50%) of OPC-67683 against mycolic acid synthesis in *M. bovis* BCG was determined and compared with that of INH, a well-known inhibitor of mycolic acid synthesis. ^{14}C-labeled acetic acid was incorporated to mycolic acid by incubation with *M. bovis* BCG cell cultures in the presence of OPC-67683 or INH as a reference. ^{14}C-labeled fatty acid and mycolic acid subclasses were detected using thin-layer chromatography (TLC, $n = 3$), and analyzed by BAS-2500 (Fujifilm). The radioactivity of each fatty acid and mycolic acid subclasses was calculated using photo-stimulated luminescence, expressed as the percentage of incorporation in untreated controls, and statistical analysis was conducted by linear regression analysis to calculate IC_{50} values and 95% confidence intervals (significance level: 5%).

OPC-67683 inhibited the synthesis of methoxy and keto mycolic acid, but not the synthesis of a α-mycolic acid , while INH inhibited all mycolic acid subclasses

Matsumoto M et al, PLoS Med. 2006;3(11):e466

In Vitro Anti-Mycobacterial Activity of OPC-67683 Compared with RFP, INH, EB, Sm, CGI-17341, and PA-824

Type Strain	MIC (μg/ml)						
	OPC-67683	RFP	INH	EB	SM	CGI-17341	PA-824
M. tuberculosis ATCC 25618 (H37Rv)	0.012	0.78	0.1	1.56	1.56	0.2	0.2
M. tuberculosis ATCC 35838 (H37Rv-R-R)	0.006	>100	0.1	1.56	0.78	0.05	0.1
M. tuberculosis ATCC 35822 (H37Rv-H-R)	0.012	0.39	>100	3.13	0.78	0.2	0.05
M. tuberculosis ATCC 35837 (H37Rv-E-R)	0.012	0.2	0.2	50	0.78	0.2	0.2
M. tuberculosis ATCC 35820 (H37Rv-S-R)	0.012	0.78	0.1	3.13	>100	0.2	0.2
M. tuberculosis ATCC 35812 (Kurono)	0.012	0.39	0.1	3.13	0.78	0.2	0.2

It shown exceptionally low MIC for M.tb

Matsumoto M et al, PLoS Med. 2006;3(11):e466

MIC_{90} of OPC-67683 against Drug-Susceptible and Drug-Resistant MTB

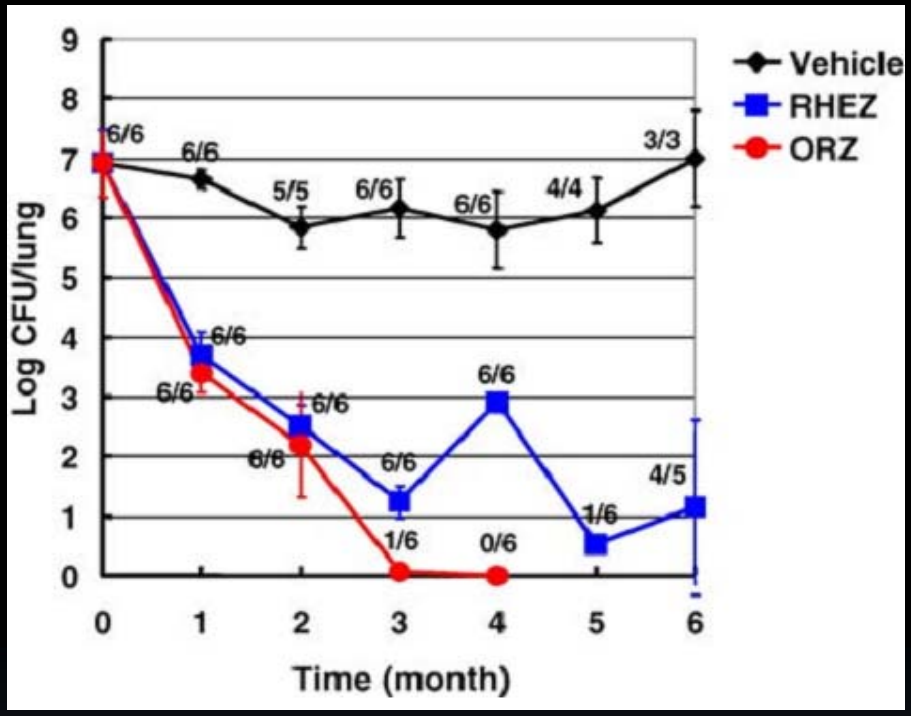
Organism Group (Number of Strains)	MIC (μg/ml)	
	MIC_{90}	95% Confidence Intervals
RFP-susceptible *M. tuberculosis* (31)	0.01248	0.01097–0.01535
RFP-resistant *M. tuberculosis* (36)	0.01221	0.01050–0.01583
INH-susceptible *M. tuberculosis* (31)	0.01194	0.01054–0.01452
INH-resistant *M. tuberculosis* (36)	0.01279	0.01094–0.01679
EB-susceptible *M. tuberculosis* (56)	0.01213	0.01081–0.01440
EB-resistant *M. tuberculosis* (11)	0.01341	0.01073–0.02450
SM-susceptible *M. tuberculosis* (49)	0.01203	0.01077–0.01416
SM-resistant *M. tuberculosis* (18)	0.0134	0.01068–0.02298

Susceptibility of OPC-67683 against 67 strains of clinically isolated *M. tuberculosis*: Resistant strains were selected based on the recommendations of the National Committee For Clinical Laboratory Standards [14] using the following criteria: 1.0 μg/ml for RFP, 1.0 μg/ml for INH, 7.5 μg/ml for EB, and 10 μg/ml for SM. We calculated the concentrations at which 90% (MIC_{90}) of the susceptible strains are inhibited. MIC_{90} and 95% confidence intervals were calculated using the actual data obtained by the probit method.

It possess highly potent activity against DS as well as DR M.tb

Matsumoto M et al, PLoS Med. 2006;3(11):e466

2ORZ+2OR vs 2HREZ+4HR in mice



Mice were inoculated intratracheally under anesthesia with 855 CFU of M. tuberculosis Kurono, and left for 28 d to allow to develop chronic TB.

After 28 d, mice were treated with ATT

The fraction refers to the number of mice in which at least one colony was detected of the total number of surviving mice

The OPC-67683-containing regimen shown:

- Rapid reduction in bacterial burdens in the first 3 months
- The organs were sterilized after 4 months
- It may reduce the treatment duration by at least 2 months

Matsumoto M et al, PLoS Med. 2006;3(11):e466

ClinicalTrials :OPC-6768

- Phase II clinical trials: 'Safety, Efficacy and Pharmacokinetics of OPC-67683 in Patients With Pulmonary Tuberculosis'
- Sponsor: Otsuka Pharmaceutical
- Locations: South Africa
- Study Type: Interventional
- Study Design:
  - Allocation: Randomized
  - Intervention Model: Parallel Assignment
  - Masking: Open Label
  - Primary Purpose: Treatment

http://clinicaltrials.gov/ct2/show/NCT00401271

- Intervention
  - Uncomplicated, smear-positive PTB patients received OPC-67683
    - Four different doses (100, 200,300 or 400 mg OD) for 14 days (No=12 patients each)
- The control group
  - Received standard therapy HREZ(No=6, Rifafour)
- Study Start Date: November 2006
- This study has been completed although the results not disclosed till date

ClinicalTrials :

- 'A Placebo-controlled, Phase II Trial to Evaluate OPC-67683 in Patients With Pulmonary Sputum Culture-positive, MDR Tuberculosis'
- Sponsor: Otsuka Pharmaceutical
- Locations: China, Egypt, Estonia, Japan, Korea, Latvia, Philippines.
- 481 patients with culture-positive resistant to H and R or only to R (conformed by positive rapid test on direct sputum) and sputum smears positive for AFB within 60 days before enrollment

http://clinicaltrials.gov/ct2/show/NCT00685360

- Intervention
  - The three treatment groups (HIV neg) for 2 months
    - Optimized Background Regimen plus 100 mg OPC-67683 twice daily (No=161)
    - Optimized Background Regimen plus 200 mg OPC-67683 twice daily (No=160)
    - Optimized Background Regimen plus placebo twice daily (No=160)
- Sputum-culture conversion
  - 5 successive weekly cultures that were negative for M. tb
  - A more sensitive culture system (MGIT) is used
- Completion Date: October 2010
- Published in
  - N Engl J Med. 2012 Jun 7;366(23):2151-60

The NEW ENGLAND JOURNAL of MEDICINE

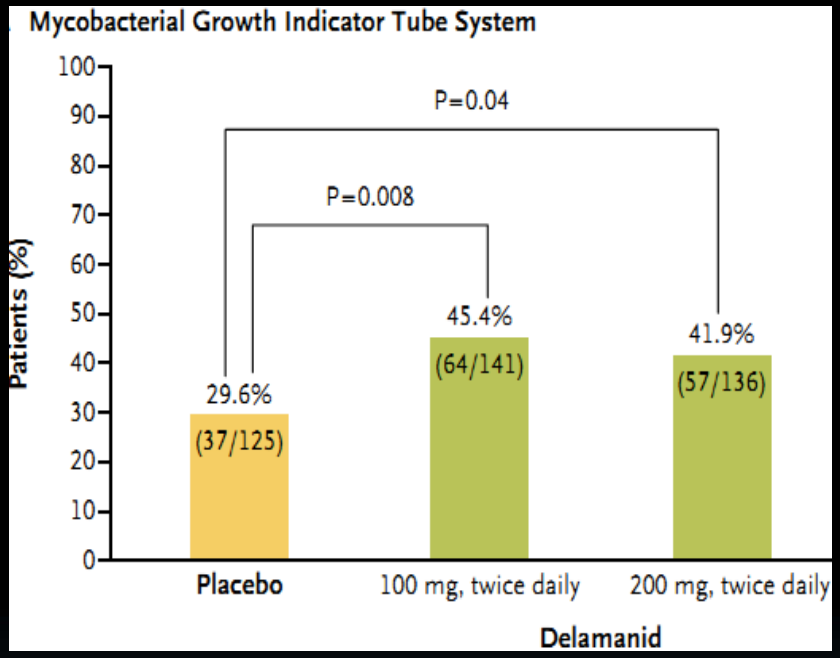
ESTABLISHED IN 1812 JUNE 7, 2012 VOL. 366 NO. 23

Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

Maria Tarcela Gler, M.D., Vija Skripconoka, M.D., Epifanio Sanchez-Garavito, M.D., Heping Xiao, M.D., Jose L. Cabrera-Rivero, M.D., Dante E. Vargas-Vasquez, M.D., Mengqiu Gao, M.D., Ph.D., Mohamed Awad, M.B., B.Ch., M.D., Seung-Kyu Park, M.D., Ph.D., Tae Sun Shim, M.D., Ph.D., Gee Young Suh, M.D., Manfred Danilovits, M.D., Hideo Ogata, M.D., Anu Kurve, M.D., Joon Chang, M.D., Ph.D., Katsuhiro Suzuki, M.D., Thelma Tupasi, M.D., Won-Jung Koh, M.D., Barbara Seaworth, M.D., Lawrence J. Geiter, Ph.D., and Charles D. Wells, M.D.

RESULTS

Among patients who received a background drug regimen plus 100 mg of delamanid twice daily, 45.4% had sputum-culture conversion in liquid broth at 2 months, as compared with 29.6% of patients who received a background drug regimen plus placebo (P=0.008). Likewise, as compared with the placebo group, the group that received the background drug regimen plus 200 mg of delamanid twice daily had a higher proportion of patients with sputum-culture conversion (41.9%, P=0.04). The findings were similar with assessment of sputum-culture conversion in solid medium. Most adverse events were mild to moderate in severity and were evenly distributed across groups. Although no clinical events due to QT prolongation on electrocardiography were observed, QT prolongation was reported significantly more frequently in the groups that received delamanid.



Sputum-Culture Conversion by Day 57

CONCLUSIONS

Delamanid was associated with an increase in sputum-culture conversion at 2 months among patients with multidrug-resistant tuberculosis. This finding suggests that delamanid could enhance treatment options for multidrug-resistant tuberculosis. (Funded by Otsuka Pharmaceutical Development and Commercialization; ClinicalTrials.gov number, NCT00685360.)

N Engl J Med. 2012 Jun 7;366(23):2151-60

ClinicalTrials:

- A Phase III, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Trial to Evaluate the Safety and Efficacy of Delamanid, has started.
- Location : Estonia, India, Latvia, Lithuania, Moldova, Republic of, Peru, Philippines, South Africa
  - Patients
    - MDR PTB Sputum Culture-positive
    - Including patients, coinfection with HIV and who are receiving antiretroviral drugs
  - Optimized Background Regimen plus 200 mg OPC-67683 daily for 6 months

- This study is currently recruiting participants
- Estimated Completion Date: September 2015

http://clinicaltrials.gov/ct2/show/NCT01424670

Oxazolidinones

- Oxazolidinones
  - PNU-100766(Linezolid), 2005 Phase II
  - PNU-100480 , 2010 Phase I
  - AZD5847 , 2009 Phase I
- Target :50S ribosomal subunit
- Mechanism of action: Inhibition of protein biosynthesis
- Resistance mechanisms: rRNA 23S mutations

PNU-100766(Linezolid)

- Linezolid was approved in 2000
  - For drug resistant, gram+ bacterial infections
  - In adults dose of 600 mg BD, 28 days with acceptable side effect.

Vinh DC et al, J Infect 2009;59:Suppl 1:S59-S74

- Data on long-term use are limited
- It has known adverse events

  (due tothe inhibition of mitochondrial protein synthesis*)
  - Neuropathies (e.g., peripheral and optic neuropathies)
  - Myelosuppression
  - Hyperlactatemia

Di Paolo A et al, Clin Pharmacokinet 2010;49:439-47

*Nagiec EE et al, Antimicrob Agents Chemother 2005;49:3896-902

- It has only modest activity in murine models of tuberculosis.

. H. Cynamon et al, Antimicrobial Agents And Chemotherapy, May 1999,1189–1191

- Case reports and retrospective studies suggest that linezolid may be effective in treating MDR and XDR tuberculosis

Anger HA et al, J Antimicrob Chemother 2010;65:775-83.

Schecter GF et al, Clin Infect Dis 2010;50:49-55.

Condos R et al, Chest 2008;134:187-92.

Eur Respir J 2009; 34: 387–393
DOI: 10.1183/09031936.00009509

A retrospective TBNET assessment of linezolid safety, tolerability and efficacy in multidrug-resistant tuberculosis

G.B. Migliori, B. Eker, M.D. Richardson, G. Sotgiu, J-P. Zellweger, A. Skrahina, J. Ortmann, E. Girardi, H. Hoffmann, G. Besozzi, N. Bevilacqua, D. Kirsten, R. Centis and C. Lange for the TBNET Study Group

ABSTRACT: Linezolid is used to treat patients with multidrug-resistant (MDR)/extensively drug-resistant (XDR)-tuberculosis (TB) cases, although clinical data on its safety, tolerability and efficacy are lacking.

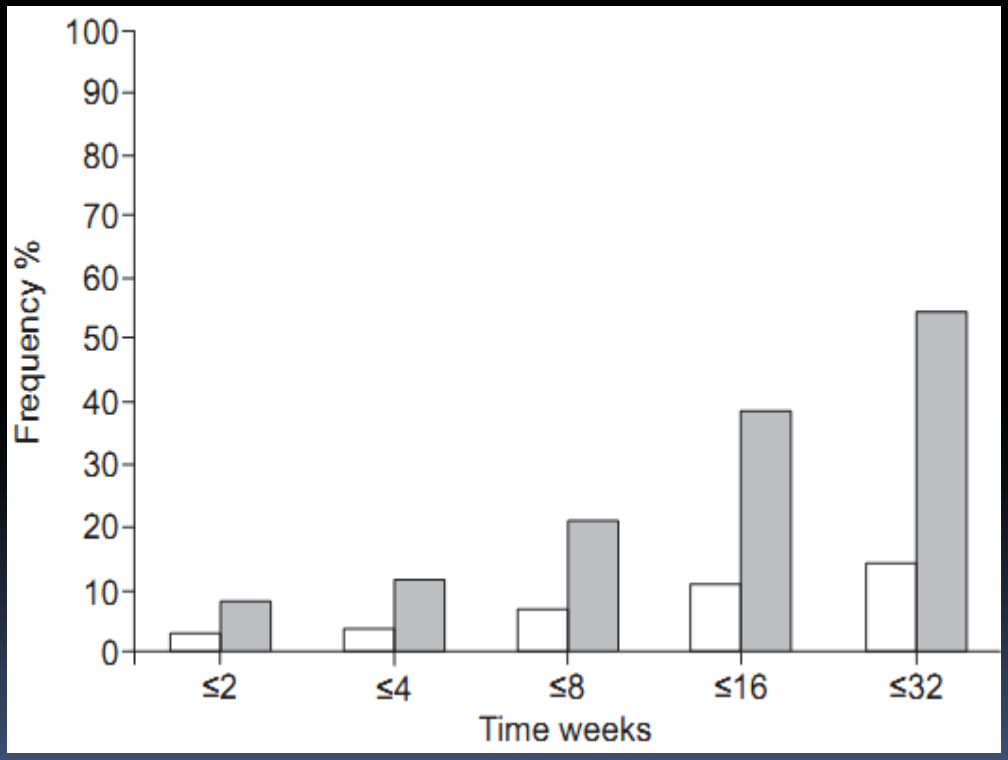
We performed a retrospective, nonrandomised, unblinded observational study evaluating the safety and tolerability of linezolid at 600 mg *q.d.* or *b.i.d.* in MDR/XDR-TB treatment in four European countries. Efficacy evaluation compared end-points of 45 linezolid-treated against 110 linezolid-nontreated cases.

Out of 195 MDR/XDR-TB patients, 85 were treated with linezolid for a mean of 221 days. Of these, 35 (41.2%) out of 85 experienced major side-effects attributed to linezolid (anaemia, thrombocytopenia and/or polyneuropathy), requiring discontinuation in 27 (77%) cases. Most side-effects occurred after 60 days of treatment. Twice-daily administration produced more major side-effects than once-daily dosing ($p=0.0004$), with no difference in efficacy found. Outcomes were similar in patients treated with/without linezolid ($p=0.8$), although linezolid-treated cases had more first-line ($p=0.002$) and second-line ($p=0.02$) drug resistance and a higher number of previous treatment regimens (4.5 *versus* 2.3; $p=0.07$).

Linezolid 600 mg *q.d.* added to an individualised multidrug regimen may improve the chance of bacteriological conversion, providing a better chance of treatment success in only the most complicated MDR/XDR-TB cases. Its safety profile does not warrant use in cases for which there are other, safer, alternatives.

Eur Respir J 2009; 34: 387–393

□: 600 mg *q.d.*, n=28; ■: 600 mg *b.i.d.*, n=57



Frequency of adverse effects attributed to linezolid

Comparison of efficacy end-points for the treatment of multidrug-resistant/extensively drug-resistant tuberculosis with or without linezolid in cases with known outcome

TABLE 2 Comparison of efficacy end-points for the treatment of multidrug-resistant/extensively drug-resistant tuberculosis with or without linezolid in cases with known outcome

	Linezolid	No linezolid	p-value
Patients n	45	110	
Sputum smear conversion time days			
Mean±SD	102.9±74	65.4±80.1	0.007
n (%)	31 (69)	59 (54)	
Culture conversion time days			
Mean±SD	109±71	69±63	0.0007
n (%)	39 (87)	86 (78)	
Treatment outcome			
Success	36 (80.0)	90 (81.8)	0.88
Cured	23 (51.1)	75 (68.2)	0.04
Completed	13 (28.9)	15 (13.6)	0.02
Failure		1 (0.9)	
Death	9 (20)	19 (17.3)	0.65

Eur Respir J 2009; 34: 387–393

- A prospective study of was carried out in LRS, Delhi, India
- 29 MDR-TB treatment failure cases included
  - 16 XDR-TB (laboratory-proven)
  - 13 MDR-TB(resistance to any quinolone but sensitive to injectables)
- All patients received daily unsupervised therapy with linezolid (Median 6 drugs)
- Out of29 pts
  - 89.7% patients achieved sputum smear and culture conversion
  - The outcome of 16 XDR-TB was comparable to the other 13 MDR-TB
- Linezolid was stopped in 3 (10.3%) patients due to adverse reactions.
- Linezolid is an effective, cheap and relatively safe drug for patients failing MDR-TB treatment, including confirmed XDR-TB

Singla R et al, Eur Respir J. 2012 Apr;39(4):956-62

- But all these studies have important limitations
  - Retrospective design
  - Small numbers
  - The use of linezolid with multiple other active agents
  - No controls
  - Limited follow-up.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis

Myungsun Lee, M.D., Jongseok Lee, Ph.D., Matthew W. Carroll, M.D., Hongjo Choi, M.D., Seonyeong Min, R.N., Taeksun Song, Ph.D., Laura E. Via, Ph.D., Lisa C. Goldfeder, C.C.R.P., Eunhwa Kang, M.Sc., Boyoung Jin, R.N., Hyeeun Park, R.N., Hyunkyung Kwak, B.S., Hyunchul Kim, Ph.D., Han-Seung Jeon, M.S., Ina Jeong, M.D., Joon Sung Joh, M.D., Ray Y. Chen, M.D., Kenneth N. Olivier, M.D., Pamela A. Shaw, Ph.D., Dean Follmann, Ph.D., Sun Dae Song, M.D., Ph.D., Jong-Koo Lee, M.D., Dukhyoung Lee, M.D., Cheon Tae Kim, M.D., Veronique Dartois, Ph.D., Seung-Kyu Park, M.D., Sang-Nae Cho, D.V.M., Ph.D., and Clifton E. Barry III, Ph.D.

N Engl J Med 2012;367:1508-18

BACKGROUND

Linezolid has antimycobacterial activity in vitro and is increasingly used for patients with highly drug-resistant tuberculosis.

METHODS

We enrolled 41 patients who had sputum-culture–positive extensively drug-resistant (XDR) tuberculosis and who had not had a response to any available chemotherapeutic option during the previous 6 months. Patients were randomly assigned to linezolid therapy that started immediately or after 2 months, at a dose of 600 mg per day, without a change in their background regimen. The primary end point was the time to sputum-culture conversion on solid medium, with data censored 4 months after study entry. After confirmed sputum-smear conversion or 4 months (whichever came first), patients underwent a second randomization to continued linezolid therapy at a dose of 600 mg per day or 300 mg per day for at least an additional 18 months, with careful toxicity monitoring.

RESULTS

By 4 months, 15 of the 19 patients (79%) in the immediate-start group and 7 of the 20 (35%) in the delayed-start group had culture conversion (P=0.001). Most patients (34 of 39 [87%]) had a negative sputum culture within 6 months after linezolid had been added to their drug regimen. Of the 38 patients with exposure to linezolid, 31 (82%) had clinically significant adverse events that were possibly or probably related to linezolid, including 3 patients who discontinued therapy. Patients who received 300 mg per day after the second randomization had fewer adverse events than those who continued taking 600 mg per day. Thirteen patients completed therapy and have not had a relapse. Four cases of acquired resistance to linezolid have been observed.

CONCLUSIONS

Linezolid is effective at achieving culture conversion among patients with treatment-refractory XDR pulmonary tuberculosis, but patients must be monitored carefully for adverse events. (Funded by the National Institute of Allergy and Infectious Diseases and the Ministry of Health and Welfare, South Korea; ClinicalTrials.gov number, NCT00727844.)

N Engl J Med 2012;367:1508-18

PNU-100480

- In Murine Model
  - PNU-100480 was more active than linezolid
  - Its efficacy increased with an escalation of the dose
  - Its activity was similar to that of H and/or R

M. H. Cynamon et al, Antimicrobial Agents And Chemotherapy, May 1999, P. 1189–1191

Williams KN et al, Antimicrob Agents Chemother 2009;53:1314–1319.

- A combination therapy with PNU-100480, moxifloxacin and pyrazinamide was more efficient than the standard treatment of HRZ
- PNU-100480 has the potential to shorten treatment of tuberculosis

Williams et al. Antimicrobial Agents Chemother 2009;53(4):1314–9.

Addition of PNU-100480 to First-Line Drugs Shortens the Time Needed to Cure Murine Tuberculosis

Kathy N. Williams[1], Steven J. Brickner[2]*, Charles K. Stover[3]†, Tong Zhu[2], Adam Ogden[2], Rokeya Tasneen[1], Sandeep Tyagi[1], Jacques H. Grosset[1], and Eric L. Nuermberger[1]

[1]Center for Tuberculosis Research, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Pfizer Inc., Groton, Connecticut; and [3]Pfizer Inc., Kalamazoo, Michigan

Methods: Following aerosol infection with *Mycobacterium tuberculosis* H37Rv and a 13-day incubation period, control mice were treated with the first-line regimen while test mice received the same regimen with PNU-100480 or linezolid added for the first 2 or 4 months. Efficacy was assessed on the basis of quantitative cultures of lung homogenates performed monthly during treatment and 3 months after completion of 3, 4, 5, or 6 months of treatment to determine the relapse rate.

Measurements and Main Results: After 2 months of treatment, mice receiving PNU-100480 in addition to the first-line regimen had lung CFU counts two orders of magnitude lower than control mice receiving the first-line regimen alone. Relapse rates after 4 months of treatment were 90, 35, and 5% when PNU-100480 was added to the first-line regimen for 0, 2, and 4 months, respectively. When the total treatment duration was 3 months, relapse rates were 85 and 35 to 45% when mice received PNU-100480 for 2 and 3 months, respectively; all control mice remained culture positive at the time of treatment completion with 17 to 72 CFU per lung. Addition of linezolid to the first-line regimen had an antagonistic effect resulting in higher CFU counts and failure to render mice culture-negative in 4 months of treatment.

Conclusions: Together with previous findings, these results confirm that PNU-100480, which is now in Phase I clinical testing, has sterilizing activity in the murine model and suggest that it may be capable of shortening treatment duration for drug-susceptible as well as drug-resistant tuberculosis in humans.

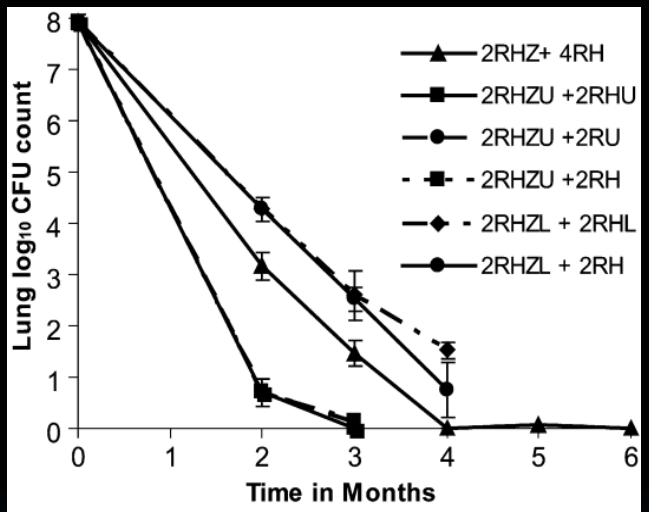


Figure 1. Change in lung CFU counts during treatment.

Am J Respir Crit Care Med Vol 180. pp 371–376, 2009

TMC207 (bedaquiline)

- Quinoline derivative: Diarylquinoline
- Long half-life
- Target : c subunit of ATP synthase
- Mechanism: inhibition of ATP synthase and disruption of membrane potential
- Resistance : atpE mutations
- It also has some additional unknown targets or resistance mechanisms

- Human mitochondrial ATP synthase displays more than 20,000-fold lower sensitivity for TMC207 as compared to mycobacterial ATP synthase
- TMC207 may not elicit ATP synthesis-related toxicity in mammalian cells

Haagsma AC et al, Antimicrob Agents Chemother 2009, 53:1290-1292.

- The drug is active on mycobacterial ATP synthesis both at neutral as well as acidic pH
- It has no significant change in affinity between pH 5.25 and pH 7.5

Anna C. Haagsma et al, PLoS ONE, 2011, 6(8): e23575.

- De novo ATP synthesis is essential for the viability of non-replicating mycobacteria (NRM)
- TMC-207 demonstrated a high bactericidal activity against the NRM.
- TMC-207 has unique dual bactericidal activity, with equal potency on replicating and dormant bacilli.

Rao SP et al, Proc Natl Acad Sci USA 2008, 105:11945-11950

- Co-administration may be difficult with CYP3A4 inducer drugs
- As the drug is metabolized by the cytochrome P450 isoenzyme CYP3A4

Matteelli A et al, Future Microbiol 2010, 5:849-858

- TMC-207 is very potent against both DS and DR M. tb strains exhibiting MIC equal to or lower than H and R

- In the murine model of tuberculosis:
  - It is as active as the combination of HRZ
  - The addition of it to HRZ regimen results in accelerated clearance of bacilli

Andries K etal, Science 2005;307:223-7

  - It also enhances the antibacterial activity of second-line drug combinations.

Lounis N et al, Antimicrob Agents Chemother 2006;50:3543-7.

ClinicalTrials:TMC207

- A Phase II, Placebo-controlled, Double-blind, Randomized Trial to Evaluate the Anti-bacterial Activity, Safety, and Tolerability of TMC207 in Subjects With Newly Diagnosed Sputum Smear-positive Pulmonary MDR-TB.
- Sponsor: Janssen Infectious Diseases BVBA
- Location Countries:
  - Brazil, India, Latvia, Peru, Philippines, Russian Federation, South Africa, Thailand
- Recruitment Status: Completed
- Enrollment: 208
- Completion Date: January 2012

http://clinicaltrials.gov/ct2/show/NCT00449644

- Intervention
  - Stage I: 8 wks (exploratory stage , No=50 pt)
  - Stage II: 24 wks (proof-of-efficacy stage, No =150 pt)
    - Drug: TMC207,400mg (4 tabs) QD for 14 days, 200mg (2 tabs) 3 times/wk for 6 or 22 wks on top of a BR
    - Drug: Placebo4 tabs QD for 14 days, 2 tabs 3 times/wk for 6 or 22 wks on top of a BR

- After the double-blind treatment phase in both Stage 1 and Stage 2, patients were continue to receive MDR-TB treatment as per national treatment guidelines.
- They were followed for safety, tolerability, pharmacokinetics, and microbiological efficacy for 96 weeks after receiving their last dose of TMC207 or placebo.
- Publications: The first stage of this study(South Africa)
  - Diacon AH et al, N Engl J Med. 2009 Jun ;360(23):2397-405.

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The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis

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METHODS

In the first stage of a two-stage, phase 2, randomized, controlled trial, we randomly assigned 47 patients who had newly diagnosed multidrug-resistant pulmonary tuberculosis to receive either TMC207 (400 mg daily for 2 weeks, followed by 200 mg three times a week for 6 weeks) (23 patients) or placebo (24 patients) in combination with a standard five-drug, second-line antituberculosis regimen. The primary efficacy end point was the conversion of sputum cultures, in liquid broth, from positive to negative.

RESULTS

The addition of TMC207 to standard therapy for multidrug-resistant tuberculosis reduced the time to conversion to a negative sputum culture, as compared with placebo (hazard ratio, 11.8; 95% confidence interval, 2.3 to 61.3; P=0.003 by Cox regression analysis) and increased the proportion of patients with conversion of sputum culture (48% vs. 9%). The mean $\log_{10}$ count of colony-forming units in the sputum declined more rapidly in the TMC207 group than in the placebo group. No significant differences in average plasma TMC207 concentrations were noted between patients with and those without culture conversion. Most adverse events were mild to moderate, and only nausea occurred significantly more frequently among patients in the TMC207 group than among patients in the placebo group (26% vs. 4%, P=0.04).

CONCLUSIONS

The clinical activity of TMC207 validates ATP synthase as a viable target for the treatment of tuberculosis. (ClinicalTrials.gov number, NCT00449644.)

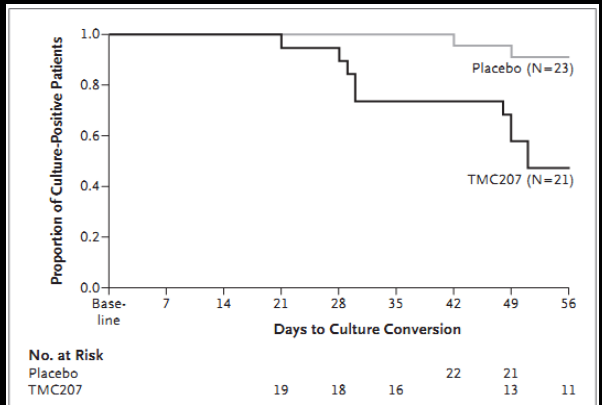

Figure 2. The Proportion of Patients with Positive Sputum Cultures and Time to Conversion.

Proportions of positive cultures were determined according to the mycobacteria growth indicator tube (MGIT) system.

Adverse Event	TMC207 (N = 23)	Placebo (N = 24)
	no. (%)	
Gastrointestinal		
Nausea	6 (26)	1 (4)
Diarrhea	3 (13)	1 (4)
Vomiting	1 (4)	2 (8)
Abdominal pain	0	2 (8)
Deafness		
Unilateral	3 (13)	5 (21)
Bilateral	2 (9)	3 (12)
Musculoskeletal and connective tissue		
Arthralgia	4 (17)	3 (12)
Extremity pain	2 (9)	4 (17)
Back pain	0	3 (12)
Respiratory		
Hemoptysis	3 (13)	4 (17)
Pleuritic pain	2 (9)	0
Chest pain	2 (9)	4 (17)
Pharyngolaryngeal pain	1 (4)	2 (8)
Cutaneous		
Rash	2 (9)	4 (17)
Pruritus	2 (9)	2 (8)
Central nervous system		
Dizziness	3 (13)	2 (8)
Headache	2 (9)	2 (8)
Hyperuricemia	4 (17)	3 (12)
Infections	3 (13)	5 (21)
Eye disorders	3 (13)	1 (4)
Reproductive system and breast disorders	1 (4)	3 (12)

* The adverse events include those reported by at least two patients in either treatment group during the double-blind treatment period, regardless of severity or causality. P=0.04 for nausea; P>0.05 for all other adverse events.

N Engl J Med 2009;360:2397-405

- TMC 207 got FDA approval for MDR TB
- Phase III clinical trials initiated

Ethylenediamine: SQ109

- SQ109 : a novel [1,2]-diamine-based ethambutol analog
- Target : unknown
- Resistance : unknown
- Mechanism:
  - No data on the mode of action are available
  - The target remains elusive as no effect of EmbA or EmbB mutation (the targets of E)

Boshoff HI et al, J Biol Chem 2004, 279:40174-40184.

- The oral bioavailability in mice was 4%
  - But it displayed a large volume of distribution into various tissues.
  - The highest concentration of SQ109 was present in lung (4MIC), which was at least 120-fold (p.o.) and 180-fold (i.v.) higher than that in plasma.

- SQ109 showed potency and efficacy in inhibiting intracellular M. tb similar to H, but superior to EMB

Lee Jia et al, British Journal of Pharmacology (2005) 144, 80–87

- The combination of SQ109 with TMC207 improved an already excellent MIC of TMC207 for M. Tb(H37Rv) by 4–8-fold

Reddy VM et al, Antimicrob Agents Chemother 2010, 54:2840-2846.

- SQ109 is in phase I/II clinical trials.

Rifapentine

- Rifapentine, a analogue rifampicin but
  - It is more potent
  - Has longer half-life
  - It is a candidate for shortening TB treatment

Rosenthal IM et al, PLoS Med 2007, 4:e344

- However, it also induces the expression of P450 enzymes.
- Phase II clinical trials are in progress to assess the effects of
  - High doses of rifapentine, given with moxifloxacin, once or twice per week
  - Daily rifapentine in the first line regimen to shorten treatment.

Lienhardt et al, Lancet 2010, 375:2100-2109.

- Rifapentine 600 (with H 900) once a week in CP, is safe and effective for treatment of PTB in HIV-negative people without cavitation on CXR.

Lancet 2002; 360: 528–34

- In mouse model of tuberculosis
  - Regimens including rifapentine and Z may dramatically shorten tuberculosis therapy whether they are combined with H or moxifloxacin

Ian M. Rosenthal, Am J Respir Crit Care Med Vol 178. pp 989–993, 2008

- Murine model LTBI treatment
  - Demonstrates that daily rifapentine-containing regimens(RPT, RPT+H,RPT+Z, RPT+H+Z)are more effective than currently recommended LTBI regimens
  - It may effectively treat LTBI in 6 to 8 weeks

Tianyu Zhang et al, Am J Respir Crit Care Med Vol 180. pp 1151–1157, 2009

SUMMARY

- Moxifloxacin is promising drug to short the duration of PTB ,Phase III trial
- PA-824 may suitable for DS & DR PTB, Phase II trial
- OPC-67683 (Delamanid) for MDR PTB under Phase III trial
- Oxazolidinones are under Phase I/II trial
- TMC 207 got FDA approval for MDR TB and Phase III clinical trials initiated
- SQ109 is in phase I/II clinical trials
- Rifapentine may shorten the duration of treatment, phase II trial